Remarks

A. Status of the Claims

Claims 20-22, 24, 26-29, 31 and 33 were pending for purposes of the Office Action and remain in the application, as amended herein, in accordance with the foregoing claim listing. Claims 1-19, 23, 25, 30, 32 and 34-38 were previously canceled without prejudice.

With regard to the claim amendmentsin this Reply, independent Claims 20 and 27 have first been amended to correct the omission of underlining for the term "vitamin D" previously intended to be added to the claims. The Examiner's recognition of this typographical error and consideration of the claim as if the term was included (though not appropriately underlined), is greatly appreciated. As stated in the previous Reply, support for this recitation is found in the specification, e.g., at page 9, lines 13-21, page 12, lines 2-6, and page 18, line 25 through page 19, line 30.

In addition, Claims 20 and 27 have been amended to specify that the analogs, salts, or derivatives of 25(OH)D are the alkylated, glycosylated, arylated, halogenated, hydroxylated or orthoesterified analogs, salts, or derivatives thereof. Support for this amendment is provided in the specification at page 18, lines 25, et seq., as kindly pointed out by the Examiner at page 6 of the current Office Action.

Finally, the independent claims 20 and 27 have been further amended to more accurately specify the effective amount of 25-hydroxyvitamin D (or its analogs, salts or derivatives) administered to the patient. Specifically, the effective amount is recited as an amount which provides specific serum levels of 25-hydroxyvitamin D or its analogs, salts or derivatives. Support for this amendment (also acknowledged by the Examiner) is found at page 18, lines 1-5 of the specification.

Applicant respectfully submits that no new matter is added by virtue of these amendments.

Withdrawal of previous rejections

Applicants gratefully acknowledge the Examiner's careful consideration of the previous amendments and remarks, as well as the Rule 132 Declaration submitted by Dr.

Schwartz. The prior submission is acknowledged as overcoming the previously cited obviousness and written description rejections.

Certain new rejections have been asserted in the instant Office Action. These new rejections are addressed in detail, below.

New Rejections – 35 U.S.C. §112

Applicants appreciate the Examiner's comprehensive analysis provided in the Office Action, the details of which were extremely helpful in providing guidance to the applicants and applicants' attorney for identifying the specific issues and addressing the rejections set forth in the Office Action. Despite the extensive discussion provided in the Office Action, however, it is believed that the interrelation of the issues allows for relatively minor claim amendments to simplify the claims and thereby adequately address and overcome all of the rejections.

1. *Indefiniteness Rejection*

Beginning at page 3 of the instant Office Action, claims 20-22, 24, 26-29, 31 and 33 are rejected under 35 USC §112, second paragraph, for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the term "effective amount" is cited as not being defined by the claim. Moreover, the Office Action states that it is not clear whether the "effective amount" refers to the 25-hydroxyvitamin D being administered or, alternatively, to the 25-hydroxyvitamin D in the target organ while not raising systemic 1,25-dihydroxyvitamin D above its "normal" range. The Examiner has concluded that the interpretation should be an effective amount is the amount effective to increase 25(OH)D in the target organ.

This interpretation is not incorrect; however, in order to make the claim more clear and definite, applicants have amended the independent claims to recite the specific amount of 25(OH)D being administered to the patient, and have now removed any reference to the amount in the target organ and to 1,25-dihydroxyvitamin D altogether. Specifically, claims 20 and 27 now provide that the "effective amount" is the amount which provides serum levels of 25-hydroxyvitamin D between about 20 and 250 nmol/L when administered to the patient. This is a known quantity that is readily determined by the ordinarily skilled practitioner. In fact, as far back as 1977, studies were published which

correlated serum levels of 25(OH)D to the amount administered (see, e.g., Stamp, et al., LANCET 1977 1:1341-1343, a copy of which is included with this submission).

The claimed serum level recited within the claims is the "normal" range defined in the specification at page 18, lines 1-4, wherein the application expressly reads that "[t]he normally observed concentration of 25(OH)D in serum is about 20-150 nmol/L … [and] up to 250 nmol/L … is considered to be normal" (citations omitted). The amended claims no longer refer to "intra-target organ cell levels of said 1,25-dihydroxyvitamin D between about 25 and about 250 nmol/L."

Applicants respectfully submit that the specific recitation of the amount of 25(OH)D administered to the patient renders the claim definite by clarifying the relative term "effective amount" and expressly relating the effective amount to the amount which raises serum levels to a particular concentration, namely, between 20 and 250 nmol/L. Reconsideration and withdrawal of the "indefiniteness" rejection under 35 USC §112, second paragraph, is respectfully requested.

2. *New Matter Rejection*

Claims 20-22, 24, 26-29, 31 and 33 also stand rejected under 35 USC §112, first paragraph. The recitation submitted as part of the January 14, 2008 amendment, *viz.*, "and results in intra-target organ cell levels of said 1,25-dihydroxyvitamin D between about 25 and about 250 nmol/L" is considered as new matter because the original claims referred to the metabolic precursor (25(OH)D) rather than the metabolite (1,25(OH_2)D). Although applicants believe the January 14, 2008 amendment is supported in the specification and is not new matter, applicants have removed the phrase in question in order to expedite the prosecution of the application toward allowance. Accordingly, the new matter rejection is moot.

In conjunction with the newly presented amendment, which now recites a defined or known amount of 25(OH)D being administered to the patient, applicants maintain that the reference to the target cell amounts of 1,25(OH_2)D are not necessary to provide definiteness to the claims. Withdrawal of this 35 USC §112, first paragraph, new matter rejection is respectfully requested.

3. Written Description Rejection

Claims 20-22, 24, 26-29, 31 and 33 further stand rejected under 35 USC §112, first paragraph, for failing to comply with the written description requirement for broadly encompassing a genus of analogs or derivatives of 25(OH)D which are not expressly recited in the specification. Applicants respectfully traverse.

As the Office Action points out, the Written Description Guidelines indicate that the "written description requirement for a claimed genus may be satisfied by a representative number of species by actual reduction to practice, or by disclosure of relevant, identifying characteristics, [etc.] by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus."

The subject application clearly provides a representative number of species, namely, the "alkylated, glycosylated, arylated, halogenated, hydroxylated or orthoesterified" analogs, salts, or derivatives of 25(OH)D, which are related to the 25(OH)D in structure and function and would be readily available to a person of ordinary skill in the art without undue experimentation. Thus, the genus as previously claimed is believed to meet the written description requirements.

Nevertheless, applicants have further amended the claims herein to recite that the genus of 25(OH)D and its relevant analogs, salts, or derivatives, is expressly defined as 25(OH)D and its alkylated, glycosylated, arylated, halogenated, hydroxylated or orthoesterified analogs, salts, or derivatives, as expressly provided in the specification. These named analogs, salts or derivatives of 25(OH)D meet the written description requirement, or at least serve as identifying characteristics of the compounds that may be used in the subject method as indicated by the Written Description Guidelines quoted in the Office Action.

Further, it is noted that the claims expressly recite that the specified analogs, salts, or derivatives are capable of being hydroxylated by a specific enzyme (vitamin D 1-alpha hydroxylase) in a target organ. This functionality is coupled with the known or disclosed correlation between structure and function and is believed to sufficiently show the applicant was in possession of the claimed genus. Therefore, applicants respectfully

submit that the written description requirement for the current claims, as amended, is clearly met. Withdrawal of the written description rejection, under 35 USC §112, first paragraph, is respectfully requested upon reconsideration.

4. *Enablement Rejection*

Finally, claims 20-22, 24, 26-29, 31 and 33 have been rejected under 35 USC §112, first paragraph, for failing to comply with the enablement requirement. Applicants respectfully traverse this rejection, especially in view of the current amendments to the claims which specify the amount of the composition to be administered and define the genus by reciting the particular species considered to be part of that genus.

The enablement rejection appears to be predicated on the recitation in the claims (prior to the current amendments) of (a) the applicants' general claim to "any" amount of prodrug (metabolic precursor) administered, and (b) the applicants' general claim to "any" analog, salt, or prodrug of 25(OH)D. Thus, the Office Action essentially asserts that the breadth of these prior claims may create an issue of undue experimentation for a person of ordinary skill to arrive at the desired amount of prodrug (25(OH)D) administered, or to determine the desired analog, salt, or derivative of that prodrug.

Applicants believe the current claims, as amended, remove these "overbroad" aspects of the invention and provide claims which are enabled by the specification because they clearly teach a person of ordinary skill in the art how to carry out the subject method without requiring experimentation that may be "undue." Specifically, the claimed method comprises administering an effective amount of a particular list of compounds. The effective amount is defined within the claim as the amount of 25(OH)D (or its alkylated, glycosylated, arylated, halogenated, hydroxylated or orthoesterified analogs, salts, or derivatives) which raises the serum levels of the compound to between about 20 and 250 nmol/L. As stated above in relation to the "indefiniteness" rejection, this amount is a known quantity that is readily determined by the ordinarily skilled practitioner.

The 1977 publication by Stamp, et al., (LANCET 1977 1:1341-1343, copy attached) teaches a correlation of serum levels of 25(OH)D to the amount administered. In particular, Figures 1 and 2, at p 1342, clearly show the effects of blood levels of 25-(OH)D in subjects receiving either long-term or short-term treatment at various doses of 25(OH)D. Thus, the levels of 25-OHD that need to be administered to achieve serum

levels of 25-OHD were clearly known to practitioners of ordinary skill in the art and are believed to be clearly enabled to perform the invention without undue experimentation.

A person of ordinary skill in the art would be able to practice the invention as now claimed without undue experimentation because the compound(s) to be administered is/ are defined and the amount being administered is defined. Thus, there is no "unpredictability" relating to carrying out the invention as claimed. Moreover, the operability of the invention is established because, as the Office Action points out in its reference to the Ma, et al., Hsu, et al., and Whitlach, et al., publications, the presence of the 1-alpha hydroxylase enzyme in the target cells will predictably convert the administered prodrug to the 1-alpha-hydroxylated metabolite.

Accordingly, the amended claims are believed to be enabled by the specification such that a rejection under 35 USC §112, first paragraph, is inapplicable. Reconsideration and withdrawal of the rejection is respectfully requested.

Conclusion

In accordance with the foregoing amendments to the claims and accompanying remarks, applicant believes the claims to meet all the requirement of 35 USC §112 and believe this case to be in condition for allowance. Such action is earnestly solicited without further delay.

Applicants further invite the Examiner to call the undersigned if clarification is needed on any aspect of this response, or if the Examiner believes a telephone interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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